

Blood Glucose Monitoring Test Systems for Prescription Point-of- Care Use

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of In Vitro Diagnostic Device Evaluation and Radiological
Health
Division of Chemistry and Toxicology Devices

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Preface

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

1 This draft guidance document describes studies and criteria that FDA recommends be used
2 when submitting premarket notifications (510(k)s) for blood glucose monitoring test systems
3 (BGMs) which are for prescription point-of-care use. When finalized, FDA intends for this
4 document to guide manufacturers in conducting appropriate performance studies and
5 preparing premarket notifications for these device types.

6
7 This guidance is not meant to address self-monitoring blood glucose test systems for OTC
8 use by lay persons. FDA is issuing another draft guidance entitled “Self-Monitoring Blood
9 Glucose Test Systems for Over-the-Counter Use” to address those device types.

10
11 FDA's guidance documents, including this guidance, do not establish legally enforceable
12 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and
13 should be viewed only as recommendations, unless specific regulatory or statutory
14 requirements are cited. The use of the word *should* in Agency guidances means that
15 something is suggested or recommended, but not required.

II. Background

Portable blood glucose monitoring test systems (glucose meters) that measure blood glucose concentrations are used by millions of people every day. These devices are currently used in a variety of clinical settings including both acute and chronic care facilities, general hospital wards and intensive care units, physicians' offices, as well as assisted living facilities and nursing homes.

Historically, the FDA has not recommended different types of information in premarket submissions (510(k)s) for blood glucose meters used by medical professionals as compared to over-the-counter self-monitoring devices intended for use by lay users. However, it has become increasingly clear that these different use settings create distinct intended use populations with unique characteristics and device design requirements. In order to distinguish between FDA recommendations for prescription use blood glucose meters, which are intended for use in point-of-care professional healthcare settings, and those intended for OTC self-monitoring by lay-persons, the Agency is issuing two separate draft guidances for (i) BGMS devices intended for use in point-of-care professional healthcare settings, and (ii) self-monitoring blood glucose test systems intended for OTC self-monitoring by lay-persons. The FDA believes that in making this distinction, each of the devices can be better designed to meet the needs of their intended use populations, thereby ensuring greater safety and efficacy.

In recent years, concerns have been raised including infection control issues related to point-of-care glucose meters. According to the Centers for Medicare and Medicaid Services (CMS) and the Centers for Disease Control and Prevention (CDC), blood glucose monitoring devices can transmit bloodborne pathogens if these devices are contaminated with blood specimens and are shared between users without effective cleaning, disinfecting and appropriate infection control measures.¹ Because BGMS devices, which are used in professional healthcare settings, are more likely to be used on multiple patients, this type of use requires certain design features and cleaning capability to prevent the spread of bloodborne pathogens².

In addition, concerns have been raised citing the inability of currently cleared BGMS devices to perform effectively in professional healthcare settings because the device's safety and effectiveness have not been evaluated for some of the intended use populations. Patients in these settings are often fundamentally different than lay users using these devices at home. Patients in professional healthcare settings can be acutely ill and medically fragile and are more likely to present physiological and pathological factors that could interfere with glucose measurements as compared to the lay population. Errors in BGMS device accuracy can lead to incorrect insulin dosing, which, when combined with other factors, can lead to increased

¹ See information at <http://www.cdc.gov/injectionsafety/blood-glucose-monitoring.html>.

² Thompson, N.D. and Perez, J.F. (2009) Eliminating the blood: Ongoing outbreaks of hepatitis B virus infection and the need for innovative glucose monitoring technologies. *Journal of Diabetes Science and Technology*. **3**(2), 283-288.

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episodes of hypoglycemia. For hospitalized patients who may be seriously ill, any inaccuracies in the meters would further increase the risk to these patients.

Previously, most blood glucose monitoring devices, even those intended to be used by healthcare professionals, were submitted to FDA with claims for OTC use. Thus, they were evaluated for self-use by diabetics, and the specific issues that occur in the professional healthcare setting were never addressed. Use of glucose monitoring devices in professional healthcare settings when they were cleared for lay use puts patients at increased risk. The performance of the devices was not evaluated in the intended use population, and the scientific and clinical issues may not have been adequately addressed for these uses. Therefore, where devices are intended for use in professional healthcare settings, distinct performance parameters should be met and sponsors should demonstrate substantial equivalence for that particular use.

In order to distinguish between prescription use blood glucose meters, which are intended for use in point-of-care professional healthcare settings, and those intended for OTC self monitoring by lay-persons, the Agency is issuing two separate draft guidances for (i) prescription use blood glucose meters, for use in point-of-care professional healthcare settings, and (ii) Self-Monitoring of Blood Glucose (SMBG) devices intended for OTC self-monitoring by lay-persons. Where before, the OTC clearance allowed automatic CLIA waived categorization (42 U.S.C. 263a(d)(3)), FDA expects that prescription-use BGMS devices will generally be categorized upon clearance as moderate complexity. Where CLIA waived status is sought, sponsors should apply for a CLIA waiver determination. We recommend that sponsors follow FDA's "Recommendations: Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices" for guidance on studies to support CLIA waived status for their diagnostic devices.

III. Scope

This draft guidance document is limited to BGMSs, which are regulated under 21 CFR 862.1345.

The following product codes are within the scope of this guidance document:

CGA (glucose oxidase method)
CFR (hexokinase method)
LFR (glucose dehydrogenase method)

This document is **not** meant to address the following types of devices:

- Over-the-Counter Self-Monitoring of Blood Glucose test systems (SMBGs) intended for use by lay persons. Additional considerations (labeling or other) may be needed for OTC devices.

- Devices used to screen for and/or to diagnose diabetes (such as clinical chemistry analyzers or semi-quantitative test strips).
- Continuous glucose sensors, implanted or external (e.g., sensors within catheters).
- Non-invasive glucose measurement devices, (i.e., devices that do not require removal of a blood sample from a fingerstick or other anatomical site).
- Blood glucose test technologies labeled for use in tight glycemic control protocols.

We recommend that you contact the Division of Chemistry and Toxicology Devices in the Office of In Vitro Diagnostics and Radiological Health (OIR) if you have questions regarding alternative intended uses or similar technologies.

IV. Reducing the Risk of Bloodborne Pathogen Transmission

Because BGMS devices use blood specimens for glucose measurement, their design and instructions for use are very important factors in reducing the risk of bloodborne pathogen transmission during use. This is especially important for blood glucose meters used in professional settings which may be used in the care of multiple patients. According to the Centers for Medicare and Medicaid Services (CMS) and the Centers for Disease Control and Prevention (CDC), blood glucose monitoring devices can transmit bloodborne pathogens such as viral hepatitis, if these devices are contaminated with blood specimens and are shared between users without effective cleaning and disinfection³. You should address the following regarding device design and labeling:

- Meters should be designed such that all external materials can be cleaned (removal of organic soil) and disinfected (microbicidal process).
- All external surfaces of the meter, including seams and test strip port, should be designed for both ease of use and ease of cleaning and disinfection.
- You should develop an effective disinfection method. You should provide the validated cleaning and disinfection procedures for your BGMS device in your submission as well as in the labeling. Cleaning and disinfection are different processes and need separate validation procedures and specifications.
- You should validate the use of any disinfectant you recommend for use with your device, as described in more detail below. We recommend you consult the Environmental Protection Agency's (EPA) list of disinfectants that are registered for use against infectious bacteria and viruses in choosing disinfectants to validate for use with your device.⁴

³ "Infection Prevention during Blood Glucose Monitoring and Insulin Administration"
<http://www.cdc.gov/injectionsafety/blood-glucose-monitoring.html>

⁴ Selected EPA-registered Disinfectants <http://www.epa.gov/oppad001/chemregindex.htm>

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- You should emphasize in the labeling that lancing devices are for single patient use and should NEVER be used for more than one person. Your BGMS device should be intended for use with only auto-disabling, single use lancing devices. The auto-disabling, single use lancing device you recommend should be specified in your labeling. [809.10(b)(ii)] Single use lancing devices are designed to be used only once, after which the blade is retracted, capped, or otherwise made unusable. Your labeling should instruct users to discard lancing devices in designated sharps containers.
- Labeling concerning safe device use can reduce the risk of user error, therefore, instructions for cleaning and disinfection should be clear and detailed. Labeling for all test system components should incorporate the same proprietary device name (ABC blood glucose test system, ABC blood glucose meter, ABC blood glucose test strips, etc.). See **Section IX-Labeling**, below for detailed labeling recommendations.

Validation of cleaning and disinfection procedures involves both validation that the cleaning and disinfection products are effective against the primary viruses of concern (HIV, Hepatitis B, Hepatitis C) and validation that the cleaning and disinfection procedures do not deteriorate the device or alter device performance. FDA recommendations for such validation procedures are outlined in the following sub-sections.

A. Validated cleaning and disinfection procedures

You should select cleaning and disinfection products that do not result in physical deterioration of the device overall, or any device component such as the housing, touch pad, or buttons. You should make note of these physical indicators during your validation study and provide this information for our review. The disinfectant product you choose should be effective against HIV, Hepatitis C, and Hepatitis B viruses. Hepatitis B virus is the more difficult to kill. Outbreak episodes associated with glucose monitors have been due to transmission of Hepatitis B viruses. Please note that 70% ethanol solutions are not effective against viral bloodborne pathogens, and the use of 10% bleach solutions may lead to physical degradation of your device.

To demonstrate that your disinfection protocol is effective against Hepatitis B virus you should perform disinfection efficacy studies to demonstrate that your procedure is effective with the external meter materials. Studies have demonstrated that viruses can remain infective for different time periods, depending on the surface. Viral survival may increase or decrease with the number of microbes present on a surface. Increasing amounts of microbes can protect viruses from disinfection, but damaging effects may also result from microbial proteases and fungal enzymes. Factors that influence survival on surfaces include fomite properties, initial viral titer, virus strain, temperature, humidity and suspending media. The simplest disinfection method would be the use of towelettes pre-saturated with a selected disinfectant. Disinfection with a towelette will reduce the risk of liquid getting into the meter, therefore minimizing the chance of affecting the glucose meter reading. However, you should choose a disinfectant that is effective against Hepatitis B Virus and compatible with your device.

We recommend you refer to the following standards:

- ASTM standard E1053-97(Reapproved 2002), Standard Test Method for Efficacy of Virucidal Agents Intended for Inanimate Environmental Surfaces
- ASTM standard E23620-09, Standard Practice for Evaluation of Pre-saturated or Impregnated Towelettes for Hard Surface Disinfection.

B. *Demonstration that the device is robust to cleaning and disinfection procedures*

You should demonstrate through bench studies that your BGMS device is robust to cleaning and disinfection procedures after multiple cleaning and disinfection cycles. You should describe in your submission the study design and results demonstrating that the analytical performance of the blood glucose monitoring system is not impacted by the cleaning and disinfection procedures.

You should address the following regarding your study design:

- You should choose worst case scenarios with regard to cleaning and disinfection frequency and end user environment to determine the number of cleaning and disinfection cycles that should be tested. For example, the number of times you clean and disinfect the meter should be representative of the cleaning and disinfection that the meter will be exposed to in its (typically 3-5 year use life).
- We recommend using the same disinfectant product for both cleaning and disinfection. The effects of using multiple cleaning products on the efficacy of disinfectant products are not well understood.
- You should demonstrate that the test strip port and all other openings are able to withstand your cleaning and disinfection procedures. The test strip port and material seams are highly susceptible to blood contamination; therefore it is important to be able to clean and disinfect these portions of your meter to reduce the risk of bloodborne pathogen transmission.
- When you evaluate your device after the cleaning and disinfection phase you should ensure that the procedure does not cloud the face/display of the meter and does not corrode or erode the plastic housing or buttons. You should note all these physical indicators throughout your study and include these results in your submission. You should evaluate the performance of the meter to ensure that repeated cleaning and disinfection does not affect performance (e.g., accuracy).
- You should include infection control in your risk analyses and incorporate your validated cleaning and disinfecting procedures into your risk assessment.

You should include a description of the protocols and acceptance criteria for all studies in your submission.

You should incorporate your labeling instructions for cleaning and disinfection in your user study (see Section VI-C) to determine the effectiveness and clarity of these instructions in your labeling.

V. Device Description

You should provide the following in the device description portion of your 510(k):

- Physical components of the system (including diagrams where appropriate).
- Manufacturer's performance specifications.
- Description and explanation of the test principle, including chemical reactions.
- Description of the format of results, including units of measure and whether results are reported in whole blood or plasma equivalents⁵.
- Description of the composition and levels of control material.
- User maintenance needs (e.g., batteries).
- Features of the device, such as data transmission capabilities or features designed to enhance robustness, including ease of use.
- Features designed to minimize the risk of bloodborne pathogen transmission among patients.

Description of features controlled by the software:

- Displays and user messages: This includes how the system determines and displays the glucose concentration; messages or displays that appear while a user is taking a measurement, and features such as how a user can retrieve past results from storage in the device.
- Error messages: This includes any error messages that the BGMS displays. Examples include displays or messages that the user sees when a strip is inserted incorrectly or removed prematurely; too small a sample is applied to the test strip; or damaged, incorrect, or deteriorated strips are used. You should also describe the error tolerance for user actions, such as these, that are inconsistent with device operation.
- User prompts: You should describe prompts that the device provides to the user, expected user responses, and timing issues (e.g., how quickly does the user need to respond, what happens if they respond after the allowed time). Examples of a user prompt are messages to the user to add specimen to the strip, insert it in the meter, calibrate the meter, or store a result.

⁵ Note that BGMS devices intended for use in the U.S. should report results in terms of plasma equivalents.

- Alarms and other feedback: You should describe how the system responds to errors in user action, user inaction, or system status, e.g., low batteries or high ambient temperature. This includes the methods by which the system detects and alerts the user when glucose levels are outside of the linear range of the system. Further, you should explain any self-diagnostic routines that the system performs.

It is important that you identify the expected responses by the user to messages. This includes whether and how the user should input information or press certain buttons to correctly set up the meter or respond to a message.

VI. Performance Evaluation for Prescription-Use BGMS Devices

Sections A-F below indicate the types of device performance information that you should include in a 510(k) submission for a BGMS device. Although many manufacturers design their BGMS validation studies based on the International Standards Organizations document 15197, FDA believes that the criteria set forth in the ISO 15197 standard do not adequately protect patients using BGMS devices in professional settings, and does not recommend using these criteria for BGMS devices.

In this section, the term “reference method” refers to a laboratory based glucose measurement method that has been well-validated for precision and accuracy, and that is traceable to a higher order, e.g., internationally recognized, reference material and/or method. The traceability chain should include as few stages as possible to reduce bias. FDA’s current thinking on the recommended study designs and device performance criteria are discussed below in Sections A-F.

A. Precision Evaluation Study

You should evaluate both repeatability and intermediate precision for your BGMS. The following sections outline FDA’s current thinking on appropriate study design and analyses to evaluate repeatability and intermediate precision for BGMS devices.

Measurement Repeatability Evaluation:

In order to assess imprecision of the device across the claimed measuring range, you should evaluate samples containing the following five glucose concentration intervals provided in the table below:

Table 1. Glucose Concentrations for Repeatability Evaluation

Interval	Glucose Concentration Range (mg/dL)
1	30-50
2	51-110
3	111-150
4	151-250
5	251-400

You should determine repeatability using venous blood samples. Altered venous blood samples such as those that are spiked, diluted, or allowed to glycolyze in order to obtain the appropriate glucose concentrations are acceptable to facilitate coverage of the entire glucose concentration range using the concentration intervals outlined in Table 1. However, you should clearly identify all altered samples (spiked, diluted, or glycolyzed) in all submitted data. A minimum of 500 test strips from at least 10 vials and 3 manufacturing lots should be used in the study. For each sample concentration, a minimum of 10 meters should be used for these studies, with at least 10 measurements taken by each meter (i.e., 100 measurements per concentration). These tests strips should be taken from the same vial and/or package for each meter.

We recommend you present the results as the mean value of the 10 measurements per meter with the corresponding standard deviation (SD) and percent coefficient of variation (CV). For each glucose concentration range in Table 1, you should also provide the mean value, standard deviation (with 95% confidence intervals) and percent CV for data combined over all meters. You should describe the statistical procedures used in the analysis. You should also include a summary of any identified outliers that were excluded from statistical analysis, the method of outlier identification and the results of these outlier investigations.

Intermediate Precision Evaluation:

Intermediate precision measurement studies are designed to measure imprecision under normal conditions of use by the intended user (i.e., measurement by individuals over multiple days, with the same meter, and reagent system lot). These studies should be performed with prepared materials, such as control materials for use with the BGMS device.

The total number of meters and individual users in these studies is at the discretion of the sponsor, however a minimum of 10 devices should be used for each concentration. Precision should be evaluated over a minimum of 10 days, taking at least 1 measurement per day of a sample from each glucose concentration interval listed in Table 1, for a minimum of 10 measurements per meter for each concentration (and 100 measurements per concentration) . You should use a minimum of 500 test strips from a minimum of 10 vials or packages and 3 manufacturing lots. These tests strips should be taken from the same vial and/or package for each meter. The study should demonstrate acceptable precision for all lots, users and meters.

You should present data including the mean value of the measurements per meter with the corresponding standard deviation (SD) and percent coefficient of variation (CV). For each glucose concentration in Table 1 you should also present the mean value, standard deviation (with 95% confidence intervals) and percent CV for data combined over all meters. You should describe the statistical procedures you use. You should provide results based on all data. If any outliers were excluded from any of your statistical analyses, you should fully describe the method of outlier identification and the results of these outlier investigations.

B. Linearity Evaluation Study

You should evaluate the linearity of your device across the entire intended measuring range. We recommend that studies include an evaluation of at least 11 evenly spaced concentrations tested and analyzed according to the guideline “Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach”, CLSI document EP6-A. Linearity studies should be performed using venous blood samples. Altered venous blood samples such as those that are spiked, diluted, or glycolyzed are acceptable to facilitate coverage of the entire glucose concentration range. You should clearly identify all altered samples (spiked, diluted, or glycolyzed) within the submitted data.

You should submit a detailed description of the study design, target concentrations, a list of all data collected in this study, summary of the results and conclusions drawn from the study, and a description of the statistical analysis used.

C. Method Comparison/User Evaluation

1. General Study Design

When testing samples from the intended patient population, you should design your study to accurately reflect the device performance in the hands of the intended operator. You should perform a set of comprehensive clinical evaluations to assess system accuracy to support the professional use of these devices in the intended use population.

FDA recognizes that most study evaluations performed for pre-market submissions occur in idealized conditions, thereby potentially overestimating the total accuracy of the BGMS device, even when performed in the hands of the intended user. Nonetheless, it is important that you design your study to most accurately evaluate how the device will perform in the intended use population. Therefore, the study should be conducted in actual conditions that reflect the expected use of the device. These conditions should be consistent with the validated environmental conditions of the device (e.g., temperature, humidity, altitude etc.). You should fully describe the conditions of your study in your pre-market submission.

You should evaluate device accuracy for each claimed sample type, for example arterial, venous, and capillary whole blood. Evaluation of each sample type should include a

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minimum of 350 patients (i.e., 350 patient samples for the arterial study, 350 patient samples for the capillary study, and 350 patient samples for the venous study)⁶. Each sample should therefore be obtained in sufficient volume to be measured on both the candidate device (i.e., new device) and the reference method.

For each claimed sample type, the samples tested should adequately span the claimed glucose measuring range of the BGMS device. Though it may be difficult to obtain samples at the extreme ends of the measuring range, the study should contain at least 10 unaltered samples < 80 mg/dL and at least 10 unaltered samples between 300 mg/dL glucose and the upper limit of the claimed measuring range of the device. If these ranges are not covered after collecting samples from 350 subjects (for each sample type), additional subjects should be enrolled until adequate sample concentrations are collected. Testing should be performed by the intended POC (point of care) user (e.g., nurses, nurse assistants, etc.) to accurately reflect device performance in POC settings; at least 9 operators should participate in each study (capillary, venous, and arterial). You should submit data from all subjects, and no subjects should be excluded from the data analysis.

The subjects you enroll in the method comparison/user study should accurately reflect the intended use population of the device. You should describe the inclusion and exclusion criteria for enrolling the study participants as well as the demographics of the subjects that participated in the study in your 510(k). If you intend to make claims for use of your meter in populations that are particularly vulnerable to potential interferences you should include patients in surgical and medical intensive care units (ICU). To collect performance data in such populations, each study should include at least 50 patient samples from the surgical ICU and 50 patient samples from the medical ICU. To obtain a representation of other patients in the hospital setting, the remaining 250 samples should be from in-patients dispersed throughout other hospital departments. You should indicate in the results which of the above categories the samples were from (surgical ICU, medical ICU, and other specified hospital departments).

If you wish to claim suitability of multiple anti-coagulants, you should include a minimum of 50 to 75 samples per claimed anti-coagulant in each of the studies described above.

You should include a minimum of 3 test strip lots and a minimum of 10 test strip vials or packages in the study. All test strips used in the study should have undergone typical shipping and handling conditions from the site of manufacture to a US user prior to the study. You should describe these shipping and handling conditions in your 510(k).

⁶ Prescription-use BGMS devices that are intended for use in a professional setting will not be automatically waived under CLIA, 42 U.S.C. 263a, so manufacturers who seek CLIA waiver for a test will need to apply for CLIA waiver. If you intend to pursue CLIA waiver for your prescription-use BGMS device, you should consider slightly increasing the study size and performing studies that are designed to support 510(k) clearance as well as CLIA waiver. Please refer to FDA's Guidance "Recommendations: Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices" for guidance on performing CLIA waiver studies. We encourage you to contact FDA to discuss this approach.

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Method comparison and user performance studies for BGMS systems include multiple users and multiple blood glucose monitoring devices. Only auto-disabling, single use lancing devices should be used in these studies. The protocol for these studies should include the detailed cleaning and disinfection procedures to follow, and the additional measures in place to mitigate the risk of potentially transmitting disease between healthcare providers, subjects and users (for example use of disposable gloves or other physical barriers). The study protocol should also include details on how often and when gloves of the trained health professionals should be changed between users. BGMS devices should be cleaned and disinfected after each subject, using validated procedures, in all studies performed. Refer to Section IV, above (Reducing the Risk of Bloodborne Pathogen Transmission) for additional information regarding the validation of cleaning and disinfecting of BGMS devices.

Blood glucose test results are used by healthcare professionals to make critical decisions about treatment; therefore, it is important that the results are accurate so that medical decision errors are better avoided. In order to demonstrate that a BGMS device is sufficiently accurate to be used safely by health care professionals, you should demonstrate that 99% of all values are within +/- 10% of the reference method for glucose concentrations ≥ 70 mg/dL, and within +/- 7 mg/dL at glucose concentrations < 70 mg/dL. To avoid critical patient management errors, no individual result should exceed +/- 20% of the reference method for samples >70 mg/dL or +/- 15 mg/dL <70 mg/dL. You should investigate and provide a justification for any BGMS test result that exceeds the above mentioned criteria and describe why the potential for that error does not render the device unsafe and ineffective, even when extrapolated to the intended use setting (e.g., when extrapolated to the volume of testing performed in the intended use setting). FDA will review the justification to determine whether the data suggests that patients may be put at risk or whether the sponsor's justification and proposed mitigation would be adequate.

Hematocrit and sodium values should be measured and recorded for each of the study participants. Blood oxygen levels should also be measured and recorded for each patient for the arterial study. You should present these individual values in the 510(k) along with the glucose meter results.

We expect that to meet the clinical needs of the user population, BGMS devices intended for prescription-use should minimally be able to measure blood glucose accurately down to 10 mg/dL and up to 500 mg/dL. The BGMS device should identify and provide an error code in situations where the measured glucose falls outside of the device's stated measuring range. For example, if meter XYZ has a measuring range that can detect glucose concentrations down to 10 mg/dL then blood samples with glucose concentrations below 10 mg/dL should provide an appropriate error code (e.g., "LOW - Less than 10").

You should describe the following in your 510(k):

- Study setting including the size, type, and location of each site and a justification of how the selected study conditions simulate intended use conditions. If only one site is used it should be representative of where BGMS devices are used in the US, and you should include an explanation of why you believe the site is representative.
- Type of study participants and the criteria used to select the participants.
- Description of the patient demographics including age, disease states, and all medications for each patient.
- Sample types collected (arterial, venous, capillary).
- Number of test strip lots, number of test strip vials, and number of meters used in the study.
- Description of the shipping and handling conditions of the test strips prior to use in the study.
- Specify how many meters per subject were used.

2. Data Analysis

You should present all data in the submission including cases in which the meter displays an error code, a 'High' or 'Low' message, or no result. All outliers that do not conform to the minimum accuracy criteria should also be included. You should investigate all outlier results and describe the results of these investigations, and explanations when possible. To assist in these investigations, you should collect information regarding patient medications, hematocrit measurements, oxygen, and sodium levels during your study. You should include the following in your description of the results:

Regression analysis:

You should present the difference between individual study subject results and the reference value (or mean of the reference value, if multiple replicates are measured on the reference method) by plotting the candidate BGMS device as the dependent variable and the reference value as the independent variable. The plot should include the regression line and line of identity, as well as the 99% confidence intervals. Your summary of results should include the slope and y-intercept, calculated using suitable regression analysis procedures and the estimate of the deviation (standard error, S_{yx}). You should describe all statistical methods used and clearly identify and describe any outliers in the analysis.

Tabular data presentation:

In addition to providing the results of regression analysis, you should also present results in the following tabular format for each sample matrix. In this table, X= the number of samples within the specified difference from the reference method, and Y= total number of samples.

Summary of data within specified mg/dL of the reference method.

Table 2. For glucose concentrations <70 mg/dL:

Within +/- 5 mg/dL	Within +/- 7 mg/dL	Within +/- 10 mg/dL	Within +/- 15 mg/dL
X/Y (%)	X/Y (%)	X/Y (%)	X/Y (%)

Table 3. For glucose concentrations ≥70 mg/dL:

Within +/- 5%	Within +/- 10%	Within +/- 15%	Within +/- 20%
X/Y (%)	X/Y (%)	X/Y (%)	X/Y (%)

Accuracy at Extreme Glucose Values:

Because the study using real patient samples may not provide a robust evaluation of the device performance in the extreme upper and lower ends of the measuring range, you should perform additional studies using blood samples altered to achieve concentrations less than 80 mg/dL and greater than 300 mg/dL glucose. These additional studies should be performed separately from the above mentioned method comparison/user performance evaluation and may be performed in a laboratory setting (e.g., at the manufacturer's facility).

You should include a minimum of 50 prepared samples with glucose concentrations <80 mg/dL and a minimum of 50 samples with glucose concentrations greater than 300 mg/dL. These samples should evenly cover the lower and upper limits of the claimed measuring range. Samples may be altered by spiking or allowing the samples to glycolyze in order to obtain the appropriate glucose concentration. Samples should be measured on both the BGMS device and the reference method. You should analyze the data using the same methods described above for the user evaluation studies. FDA will also apply the same review criteria.

Error Codes Outside the Measuring Range:

You should perform adequate analyses to demonstrate that your device provided the appropriate error codes when glucose concentrations measured were out of the device's stated measuring range, and include results in your 510(k).

Neonatal Studies:

You should perform studies to support performance in neonatal samples (defined as subjects less than 28 days old). Neonatal blood is known to differ from adult blood and these differences may have a direct impact on the safety of blood glucose monitoring. Neonatal blood often has higher hematocrit levels (51 to 65 %) and lower blood glucose concentrations (20 to 80 mg/dL) compared to adult blood.

You should evaluate device performance with neonatal samples by testing 100 to 150 fresh neonatal capillary blood specimens in direct comparison to the reference method. Samples should be collected and measured by at least three POC users in a POC setting. Glucose concentrations should be measured on the BGMS device and on the reference method, and the hematocrit levels for each patient should also be measured and reported

in the study. You should present as described above in the Data Analysis Section. Data from all subjects in the study should be submitted, and no subjects should be excluded from the data analysis.

Since it may be difficult to obtain samples at the extreme ends of the measuring range using real neonatal patient samples, in order to provide a robust evaluation of the device performance in the extreme upper and lower ends of the measuring range, you should perform additional studies using blood samples (either adult blood or maternal cord blood) altered to achieve concentrations between 10 and 50 mg/dL. Blood specimens used in these additional studies should be adjusted to at least two levels of hematocrit at or near 40% and 65%. These additional studies should be performed separately from the above-mentioned method comparison evaluation and may be performed in a laboratory setting (e.g., at the manufacturer's facility).

D. Interference Evaluation

You should evaluate the effect of potentially interfering endogenous and exogenous substances and conditions on device performance, such as icterus, lipemia, and varying hematocrit levels, as well as the effect of common medications.

1. Endogenous/Exogenous Substances

Study design:

You should perform interference testing using samples containing glucose concentrations across the range of the device. Specifically, testing should be performed in samples with glucose concentrations of 60 mg/dL, 120 mg/dL, and 250 mg/dL to evaluate clinically relevant decision points.

You should evaluate each potentially interfering substance at clinically relevant concentrations. You should test all substances at a minimum of two concentrations – the concentration that is expected or the therapeutic concentration, and the concentration that is the highest that could potentially be observed in a whole blood sample. For example, acetaminophen should be tested at an expected therapeutic concentration of 20 µg/mL and also at the high, toxic concentration of 200 µg/mL. The list below provides our recommendations on the substances and concentrations that should be tested for interference.

Table 4. List of Potential Interferents for BGMS Devices.

Interferent	Therapeutic Level	High Toxic Concentration
Acetaminophen	20 µg/mL	200 µg/mL
Ascorbic acid	0.8 mg/dL	3 mg/dL
Bilirubin	1 mg/dL	25 mg/dL
Cholesterol	154 mg/dL	309 mg/dL
Creatinine	1 mg/dL	10 mg/dL
Dopamine	20 pg/mL	200 µg/mL
EDTA	0.1 mg/mL	2 mg/mL

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Galactose	1 µg/mL	100 µg/mL
Gentisic acid	0.1 mg/mL	10 mg/mL
Glutathione	5 µmol/L	100 µmol/L
Hemoglobin	14 g/dL	20 g/dL
Heparin	0.5 IU/mL	5 IU/mL
Ibuprofen	10 µg/mL	500 µg/mL
L-Dopa	2 µg/mL	5 µg/mL
Maltose	1 mg/mL	100 mg/mL
Methyldopa	10 mg/L	10 g/L
Salicylate	100 µg/mL	500 µg/mL
Sodium	120 mEq/L	175 mEq/L
Tolbutamide	100 mg/L	1000 mg/L
Tolazamide	40 mg/L	400 mg/L
Triglycerides	100 mg/dL	500 mg/dL
Uric acid	5 mg/dL	10 mg/dL
Xylose	20 mg/dL	200 mg/dL
Sugar Alcohols*	0.03 mg/100mL	0.09 mg/100mL

* All common sugar alcohols should be tested including mannitol, sorbitol, xylitol, lactitol, isomalt, maltitol and hydrogenated starch hydrolysates (HSH). Sponsors should determine appropriate levels to test for interference with BGMS devices based upon common concentrations of these substances in the blood of diabetic patients.

You should provide a reliable estimate of the interference predicted for individual samples. To do this, we recommend the following method of measuring and calculating interference:

Each sample should be tested on the reference method in replicates (a minimum of 4). An average of reference measurements, for example, may give greater confidence in the true glucose concentration of the sample.

You should use at least three test strip lots to evaluate interference. Each test sample should be tested on the new BGMS device in replicates of 30 (10 replicates per lot of test strips, for a total of 30 replicates per sample). Each replicate should be compared to the average value from the reference method and a bias and percent bias calculated. The percent bias for each replicate should be combined to produce an average percent bias for the sample (with 95% confidence intervals).

In the rare case where the substance being evaluated for interference with the new device also interferes with the reference method, a reference sample should also be created for each substance that contains the identical glucose concentration but solvent/vehicle in lieu of the potential interfering substance. The test sample can then be compared to the reference sample value as measured by the reference method. You should provide information demonstrating interference with the reference method for each substance in this category.

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For BGMS devices, the degree of acceptable interference may vary by substance tested and applicable patient populations. Therefore, you should report in the 510(k) the observed average percent bias for each sample/substance tested and any observed trends. If interferences are observed, you should propose appropriate labeling to mitigate the risk of the interference in the patient population; the labeling language appropriate for the observed interference will be discussed during the review of the submission. We do not recommend that final labeling be printed prior to receiving FDA input during the review.

If significant interference is observed at one substance concentration but not the other, you should perform additional analyses to determine the concentration at which interference begins to occur. For example, if the observed bias is 12% at 200 µg/mL dopamine but only 2% at 20 pg/mL, additional testing should be performed to determine the lowest concentration between these two concentrations at which significant interference is observed. In the 510(k), you should provide your definition of “significant” interference for that substance.

The substances listed above in Table 4 represent known or reasonable potential interferents for current glucose measurement technologies. As new drugs are developed that may interfere with your device or new interfering substances are identified, you should evaluate them for potential interference with your device. For example, if a new drug intended to treat cardiac complications in diabetic patients is approved, you should conduct a careful evaluation to determine whether the new drug interferes with your device. You should report to FDA if significant new interferences are observed with any cleared glucose monitoring device that is on the market. New drugs/potential interferents should also be evaluated when new or significantly modified technology is introduced.

Data Analysis:

You should provide raw data sets as well as a summary table for all interference results. Please note that the summary tables should be presented separately for each test strip lot and glucose level tested. Table 5 below provides a sample format.

Table 5. Recommended Summary Table Format:

Lot 1/ Glucose Low Concentration (60 mg/dL)

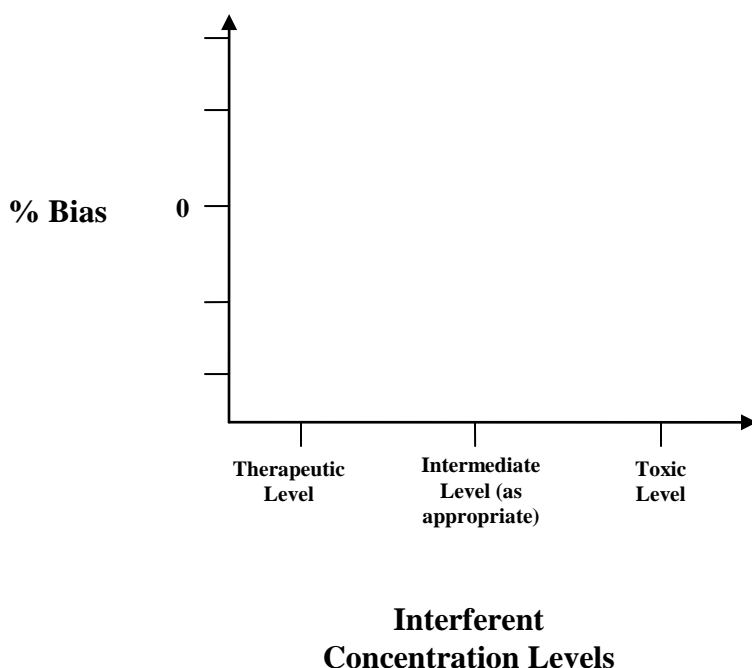
Potential Interferent: Acetaminophen

Mean Glucose Value (YSI)	Interference Level	Mean Glucose (Meter)	Bias (mg/dL)	% Bias	Confidence Interval
60 mg/dL	20 µg/mL				
	100 µg/mL				
	200 µg/mL				

We recommend you also present data graphically for each individual test strip lot. Graphs should demonstrate the percent bias for all data points included in the study at

therapeutic, toxic and any intermediate levels. The graph should also include the confidence intervals around the bias. A sample graph is shown below:

Figure 1: Format for Interference Graph



In your 510(k) you should include a detailed description of the study design, a list of all data collected in this study, the summary tables and graphs indicated above and a description of the conclusions drawn from the study.

2. Hematocrit

Study design:

You should evaluate the effect of hematocrit on the performance of your system to assess whether your device can safely be used across the claimed hematocrit range in the intended use population. The observed hematocrits may be very broad in the intended use population for this type of device; the intended patient population may reasonably be expected to have hematocrit values between 10 and 65% hematocrit. Therefore, we recommend a minimum hematocrit range of 10-65% as the claimed range for this type of device.

Because a reasonably sized method comparison study still may not include the full range of hematocrit values expected in the intended use population, you should perform a separate study to determine how much analytical error may be contributed by this condition. You should evaluate hematocrit interference by measuring samples containing various glucose concentrations in reconstituted blood. The samples should be prepared to contain designated levels of hematocrit that span the claimed hematocrit range for the device. The blood sample may be adjusted by spiking or allowing it to glycolyze to

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obtain the desired glucose concentration. Specific percentages of hematocrit may be achieved for each sample by manipulating the plasma to packed cell ratio following centrifugation. Hematocrit levels tested should span the claimed range in 5% intervals. For example, if your claimed hematocrit range is from 10-65%, you should test samples at 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60 and 65 % hematocrit. The samples should also span the claimed measuring range for blood glucose. Samples should include 5 different blood glucose concentrations evenly spread and targeted to the following ranges: 30 – 50, 51 – 110, 111 – 150, 151 – 250, and 251 – 400 mg/dL.

Each sample should be tested on the reference method in multiple replicates (a minimum of 4). An average of reference measurements, for example, may give greater confidence in the true glucose concentration of the sample.

You should test a minimum of 3 test strip lots to evaluate interference from hematocrit. Each test sample should be tested on your new BGMS device in replicates of 30 (10 replicates per lot of test strips, for a total of 30 replicates per sample). Each replicate should be compared to the average reference value for the sample and a bias and percent bias calculated. The percent bias for each replicate should be used to determine an average percent bias for the sample (with 95% confidence intervals).

Because hematocrit interference is only one of the variables that will contribute to the overall analytical error of the system, it is important that it represent only a portion of the safely allowed error for the system. For this reason, bias observed in this study should be less than 5% on average, and no individual value should be greater than 10% of the reference method.

Data Analysis:

You should provide raw data sets as well as a summary of the hematocrit interference study (see recommended format below). Please note that the summary tables should be presented separately for each test strip lot and glucose level tested.

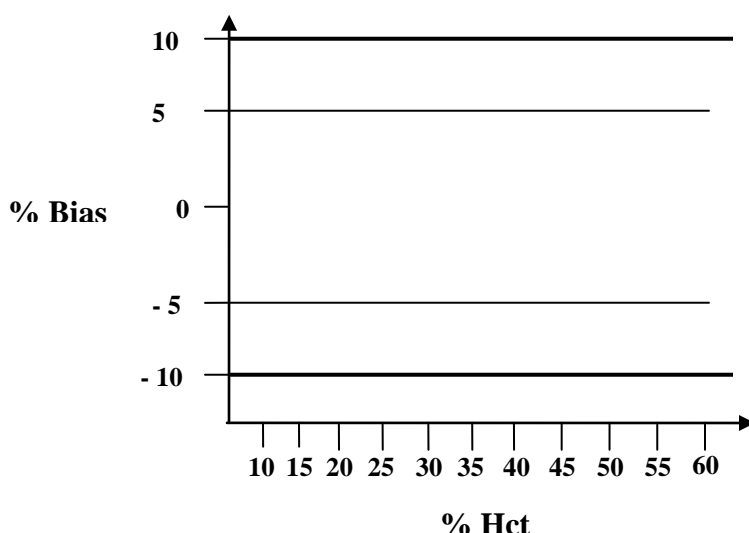
Table 6:
Sample format for hematocrit results: Lot 1; Glucose Level 1 (30 – 50 mg/dL)

Mean Glucose Value (YSI)	Hct (%)	Mean Glucose Value (Meter)	Bias (mg/dL)	% Bias	# of Observations > +/- 10% Bias

You should also present the data graphically for each individual test strip lot. Graphs should include percent bias for all data points included in the study. The graph should include confidence intervals around the percent bias.

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Figure 2. Sample format for graph of hematocrit interference



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You should submit a detailed description of the study design, a list of all data collected in this study, the summary tables and graphs indicated above, and a summary of the conclusions drawn from the study.

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3. Oxygen

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Study design:

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You should also evaluate the effect of oxygen on the performance of the device to assess whether it can safely be used across the claimed blood oxygen range in the intended use population. In the intended use population for this type of device, the observed oxygen levels in blood may be very broad; the majority of intended users may reasonably be expected to have oxygen values between 40 and 200 mmHg. Therefore, we recommend a minimum range of 40 – 200 mmHg as the claimed range for this type of device.

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Because a reasonably sized method comparison study may not include the full range of oxygen values expected in the intended population, to determine how much analytical error may be contributed by this condition you should conduct a separate interference study. You should evaluate oxygen interference by measuring samples containing various glucose concentrations in reconstituted blood that are prepared to contain designated levels of oxygen spanning the claimed range for the device. The blood samples may be adjusted via spiking or allowing the samples to glycolyze to obtain the desired glucose concentration. Specific percentages of oxygen may be achieved by altering the oxygen content of the samples. Oxygen levels tested should span the claimed range. For example, if the device's claimed oxygen range is from 40-200 mmHg, samples should be tested at 40, 45, 50, 55 mmHg. . . 190, 195 and 200 mmHg. The samples should also span the claimed measuring range for blood glucose. You should include samples at 5 different blood glucose concentrations evenly spread and targeted to the following ranges: 30 – 50, 51 – 110, 111 – 150, 151 – 250, and 251 – 400 mg/dL. Each sample should be tested on the reference method in multiple replicates (minimum of 4). An average of

reference measurements, for example, may give greater confidence in the true glucose concentration of the sample.

You should include a minimum of 3 test strip lots to evaluate interference from oxygen. Each test sample should be tested on your new BGMS device in replicates of 30 (10 replicates per lot of test strips, for a total of 30 replicates per sample). Each replicate should be compared to the average reference value for the sample and a bias and percent bias calculated. The percent bias for each replicate should be used to determine the average percent bias for the sample (with 95% confidence intervals).

Data Analysis:

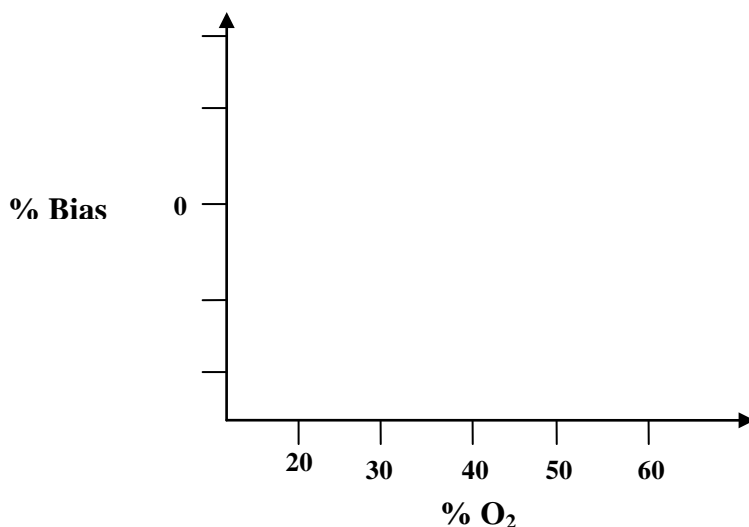
You should provide raw data sets as well as a summary of the oxygen interference study (see recommended format below). Please note that the summary tables should be presented separately for each test strip lot and glucose level tested.

Table 6. Example Table for Oxygen Interference, Lot 1; Glucose Level 1 (30-50 mg/dL)

Mean Glucose Value (YSI)	O ₂ (%)	Mean Glucose Value (Meter)	Bias (mg/dL)	% Bias

You should also present data graphically for each individual test strip lot. Graphs should include percent bias for all data points included in the study. The graph should include confidence intervals around percent bias.

Figure 3. Sample format for graph of oxygen interference



You should submit a detailed description of the study design, a list of all data collected in this study, the summary tables and graphs indicated above, and a summary of the conclusions drawn from the study.

E. Flex Studies

Generally, the risk of an erroneous result may be greater for POC tests than laboratory-based tests. This is because there are fewer controls in place in POC settings to mitigate risks and the users may be untrained and may not know how to identify or address an incorrect result. You should demonstrate that your BGMS device design is robust (e.g., insensitive to environmental and usage variation) and that all known sources of error are effectively controlled. In general, flex studies should be used to demonstrate robust design while risk management should be used to demonstrate the identification and effective control of error sources, although the two are not mutually exclusive.

Most risk control measures should be fail-safe measures or failure alert mechanisms. Examples of fail-safe mechanisms are lock-out functions to ensure that a test system does not provide a result when test conditions are inappropriate, such when there is a component malfunction or operator error. Other examples are measures within the system to prevent operator error, such as guides or channels that prevent improper strip placement. We recommend that test system design incorporate fail-safe mechanisms whenever it is technically practicable. If fail-safe mechanisms are not technically practicable for some risks, failure alert mechanisms should be used. Failure alert mechanisms notify the operator of any test system malfunction or problem. They may include measures such as internal procedural controls or electronic controls. Devices with such mechanisms allow the operator to correct the error, or put the operator on notice that the results will be unreliable due to the error. For example, in cases where the result exceeds the reportable range (e.g., extremely high or low glucose result) and the result is a critical value, the device should give a message such as "out of range high" or "out of range low."

Flex studies, or studies that stress the operational limits of a test system should be used to validate the insensitivity of the test system to performance variation under stress conditions. Where appropriate, flex studies should also be used to verify and/or validate the effectiveness of control measures at operational limits.

In order to identify all relevant flex studies for your BGMS device, we recommend that you conduct a systematic and comprehensive risk analysis that identifies all potential sources of error, including test system failures and operator errors, and identifies which of these errors can lead to a risk of a hazardous situation. You should then identify control measures, including fail-safe and failure alert mechanisms that will reduce risks for these sources of error. When the control measures have been implemented, you should (1) verify that each control measure has been properly implemented, and (2) verify and/or validate the effectiveness of each control measure. When appropriate, flex studies should be used to verify and/or validate the effectiveness of these control measures.

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Below we have identified flex studies that we believe are important for you to perform in order to demonstrate adequate performance of these types of BGMS devices. At the same time, we continue to encourage you to perform risk analyses to determine whether your device includes any unique or new features that should be validated through flex studies.

If your BGMS device does not perform adequately in flex studies, we recommend that you provide a justification, determined by means of thorough risk analysis, as to why adequate performance under that flex study is not required for safe, effective use of the device or indicate an additional validated control mechanism you have implemented to assure safe and effective use of the device. FDA will review such justifications to determine whether the proposed mitigation strategies are adequate to protect patients.

In the case of the following flex studies, it is sufficient for you to provide information indicating that flex studies have been conducted in accordance with a recognized industry standard. We recommend you include information regarding the type of testing performed, the reference standard followed, the acceptance criteria, and whether the BGMS device passed testing requirements. The flex studies we recommend performing in this manner are:

- Mechanical Vibration Testing
- Shock Testing
- Electromagnetic compatibility (EMC) Testing
- Electrostatic Discharge/Electromagnetic Interference Testing

We have also identified additional flex studies that we believe are important for manufacturers to perform in order to demonstrate adequate system performance in intended use settings. Unless otherwise indicated, we recommend that you clearly identify all flex studies performed on your device in your 510(k). A detailed description of the following attributes should be included for each study:

- Study goal
- Study protocol and methods
- Methods used to apply samples to test strips
- Description sample type and any anticoagulants used
- Study results
- Description of conclusions made from the study

The recommended flex studies as well as recommended study designs are outlined below in Sections 1-7.

1. Test Strip Stability Testing

You should perform a study to assess test strip performance throughout its claimed shelf life. We request that you submit only the study protocol, the acceptance criteria for the test strip stability study, and when applicable, the conclusions of the study.

You should evaluate precision and accuracy of test strips at various time points throughout their stated shelf life. You should indicate the time points that are assessed in this stability protocol (e.g. 1 month, 3 months, 2 years); combinations of real-time and accelerated aging studies are acceptable. You should perform both precision and accuracy evaluations at each identified time point as described below. Through these evaluations, you should demonstrate that the CV calculated in this study is within the labeled performance of the BGMS device.

Precision Evaluation:

Precision with Control Materials

This study should be completed over 5 days and use glucose controls. At least two BGMS devices should be included in this study and at least 10 measurements should be taken per control level per meter.

Precision with Whole Blood Samples

This study should be completed over 10 days using whole blood samples spanning the BGMS device's stated measuring range. Samples may be altered by spiking with glucose or allowing the samples to glycolyze in order to evaluate the extreme end of the system's measuring range. At least two BGMS devices should be included in this study and at least 10 measurements should be taken per glucose level, per meter.

Accuracy Evaluation:

The study should be performed using patient whole blood samples that span the BGMS device's stated measuring range. It is acceptable for samples to be spiked with a known concentration of glucose, or allowed to glycolyze to achieve the desired concentration in order to evaluate the extreme ends of the system's measuring range. Glucose concentrations should be measured on the BGMS meter and compared to values obtained with the reference method.

2. Temperature and Humidity Effects

Temperature and humidity studies should be performed for all BGMS devices and should be conducted with whole blood samples compared to the reference method. Tested temperature and humidity ranges should not only cover the claims specified in the device labeling, but test conditions should also stress the BGMS device and include ranges outside of labeling claims. We believe the following recommendation for conducting temperature and humidity effects studies most closely represents actual use conditions experienced by users of BGMS devices.

We recommend simultaneously evaluating temperature and humidity effects on blood glucose meters and blood glucose test strips under "Open Vial" (i.e. to mimic use of test strips after an individual user has opened a test strip vial) and "Extended Open Vial" (i.e.

to mimic use of test strips from vials that have been left completely open for the duration of the claimed test strip vial shelf-life) conditions. Separate testing of test strip and meter shipping and storage conditions are not necessary if, the temperature and humidity studies outlined here only utilize packaged blood glucose meters and blood glucose test strips that have undergone appropriate storage conditions and the longest possible shipping duration (both as specified by the manufacturer) are used. In addition, tested temperature and humidity ranges should not only cover the claims specified in the device labeling, but test conditions should also stress the BGMS device and include ranges outside of labeling claims. We recommended that you test the effects of fluctuating temperate and humidity on blood glucose meters and blood glucose test strip performance, as well as effects of heat and humidity changes across the open vial shelf life. We recommend you use multiple meters and test strip vials in these studies.

We recommend that you present results for temperature and humidity studies as the mean values of measurements per meter. You should also include corresponding SD and CV, as well as the grand mean, pooled variance, pooled standard deviation (with 95% confidence intervals) and pooled CV. You should describe your statistical methods. For statistical analysis, ANOVA is the preferred method for calculating intermediate precision. You should also include a summary of any identified outliers that were excluded from statistical analysis, the method of outlier identification and the results of outlier investigations.

We encourage manufacturers to also consider ways in which temperature and/or humidity detectors might be incorporated into test strip containers to alert users when strips have not been handled correctly or stored according to recommended and validated conditions.

3. Altitude Effects

You should evaluate the effect of altitude on performance for your BGMS by comparing results from whole blood samples with the candidate device to the reference method. These studies should include a pressure change. Studies based on oxygen tension instead of pressure change are not adequate, because oxygen tension is only one component that changes with altitude. Altitude pressure changes can be accomplished by physically increasing altitude (e.g., in an airplane, on a mountain), or by simulating increasing altitudes and atmospheric conditions in a pressurized chamber. Results should support the altitude labeling claim for your device. You should provide your definition for terms, such as “sea level”. The definition of sea level should not extend past 500 feet. You should test your BGMS device at a minimum of 10,000 feet above sea level.

4. Short Sample Detection

Blood glucose measurement from short samples (samples of reduced sample volume) can lead to inaccurate results. To avoid the risk of inaccurate results, BGMS devices should be able to detect that a short blood sample has been applied to the test strip and should not provide a result to the user. Short sample detection systems should not rely on visual verification by the user.

The volume required to classify a test sample as a short sample is dependent upon the BGMS device. In your short sample detection studies you should include blood samples with known glucose concentrations in the following three ranges: 50-65, 100-120, and 200-250 mg/dL. You should test blood samples with your candidate device at each of the glucose concentrations listed above. Blood samples with serially reduced volumes should be measured on the device until an error is either generated by the device or the test result falls outside of the device's stated performance range. Results obtained from the candidate device should be compared to the reference method. In your submission you should describe the results from both the candidate device and the reference method, as well as the sample volume tested for each of the tested glucose concentration ranges.

5. Sample Perturbation Study

Sample perturbation occurs when a user has applied an appropriate volume of blood to the test strip for glucose measurement but an event, such as wicking of blood away from the test strip, flicking of the test strip or flicking of the meter occurs during the start of measurement and alters the volume of the initial sample application. Sample perturbation often leads to a short sample.

You should adequately demonstrate how your BGMS handles sample perturbation, through a sample perturbation study. In such a study, once a sample has been applied to the test strip and the BGMS device has begun to read the sample, the test strip should be perturbed. The sample perturbation study should incorporate blood samples with known glucose concentrations in the following three ranges: 50-65, 100-120, and 200-250 mg/dL. In your 510(k) submission you should describe your protocol, including your specific method of perturbing the test sample, as well as meter results compared to the reference method.

6. Intermittent Sampling

Intermittent sampling occurs when a short sample is applied to a test strip, a glucose measurement begins, and the user adds more sample to the test strip before the glucose measurement is complete.

You should adequately demonstrate how your BGMS handles intermittent sampling by conducting a study. The intermittent sampling study should incorporate blood samples with known glucose concentrations in the following three ranges: 50-65, 100-120, and 200-250 mg/dL. You should perform intermittent sampling studies that are representative of actual events. For instance, approximately one half of the sample should be applied to the test strip prior to the start of sample measurement, then the other half of the sample should be applied to the strip once the sample starts reading. You should describe how the device responds to this scenario, including whether a result is reported by the device, whether the result is accurate (relative to the reference method) and when an error code is reported.

7. Testing with Used Test Strips

We recommend that BGMS devices be designed to automatically recognize the insertion of used test strips. Insertion of used test strips into a blood glucose meter should not provide glucose measurement results to the user. If an automatic used test strip recognition function has been incorporated into the BGMS device, you should perform a flex study to demonstrate the functionality of this recognition system. If an automatic used test strip recognition function has not been incorporated into the design of the blood glucose meter, you should perform a study to demonstrate that the insertion of used strips for glucose testing generates an error code to the user. In your submission you should provide the study protocol, acceptance criteria and results.

F. *Calibration and External Control Solutions*

We recommend you follow FDA's "Guidance for Industry and FDA Staff - Assayed and Unassayed Quality Control Material" [<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm079179.htm>] and submit the recommended information to support clearance of any assayed glucose quality control material you choose to provide with their BGMS device. For a description of more points to consider regarding calibration and quality control materials, please refer to the guidance document "In Vitro Diagnostic Devices: Guidance for the Preparation of 510(k) Submissions – Appendix K – Points to Consider for Review of Calibration and Quality Control Labeling for In Vitro Diagnostic Devices" (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094635.htm>).

You should describe how your device recognizes and distinguishes calibration or control materials from patient specimens as well as explain how the system compensates for differences between strip lots or strip types.

VII. **Test Strip Lot Release Criteria**

Your test strip lot release criteria should be sufficient to ensure consistent quality of the BGMS test strips. You should provide a description of the lot release criteria and a summary of the sampling scheme in your 510(k).

We recommend that you select a sampling scheme appropriate for the operation of your device and test each outgoing test strip lot or batch using the precision and accuracy evaluations described below. Your release criteria should be designed to ensure that all released lots conform to the labeled BGMS device performance *in the hands of the intended user*. Therefore, these criteria should be more stringent than the criteria used to evaluate total error in the user studies. Estimates of the device's imprecision and average bias may be used to determine appropriate lot release criteria. For example, if the device has an average CV of 3% and an average bias of 5%, these may be considered in determining the appropriate criteria.

Precision Evaluation:

Precision using Control Materials

This study should be completed over 5 days and use glucose controls. At least two BGMS devices should be included in this study and at least 10 measurements should be taken per control level per meter.

Precision using Whole Blood Samples

This study should be completed over 10 days using whole blood samples spanning the BGMS device's stated measuring range. Spiking samples with glucose, or including samples in which glucose was allowed to glycolyze is acceptable in order to evaluate the extreme end of the system's measuring range. At least two BGMS devices should be included in this study and at least 10 measurements should be taken per glucose level, per meter.

Accuracy Evaluation:

The accuracy evaluation should be performed using patient whole blood samples that span the BGMS device's stated measuring range. It is acceptable for samples to be spiked with a known concentration of glucose, or to include samples in which the glucose was allowed to glycolyze in order to evaluate the extreme ends of the system's measuring range. Glucose concentrations should be measured on the BGMS meter and compared to the reference method.

Third Party Test Strips:

Third party test strips refer to test strips manufactured and distributed by a company other than the company that manufactures and distributes the glucose meter. Third party test strip manufacturers should ensure that they are aware of any design changes to the meter, because such changes could affect compatibility of the strip with the meter. We strongly recommend that agreements between the third party test strip manufacturer and the meter manufacturer are in place to ensure that the third party test strip manufacturer is made aware of any design changes to the meter. In cases where this is not possible, the third-party test strip manufacturers should specify, in their submission, how they will mitigate the risk of incorrect results due to meter design changes.

VIII. Software

For software descriptions of BGMS devices, their components, and accessories, we recommend that you follow **Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices**, <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089593.pdf> . Generally, we consider glucose meters to be a moderate level of concern because glucose results will be the basis for treatment, including determination of insulin dosage by the patient or health care provider. Incorrect glucose results or failure of

the software to detect an error could result in improper therapeutic management. (Also see Section V, above regarding software descriptions in your 510(k)).

IX. Labeling

The premarket notification must include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). Final labeling must also satisfy the requirements of 21 CFR 809.10. Distinct labeling (user manual, quick guide, test strip labeling, and box labeling) appropriate for the intended user of the BGMS, should be provided for each device component.

The following items are intended to further assist you in complying with the requirements of 21 CFR 809.10 for all test strip and meter labeling. You should refer to that regulation for the complete list of labeling requirements for IVD devices.

1. The device container and the device package insert must contain the proprietary and common names of the device. 21 CFR 809.10(a)(1) and 21 CFR 809.10(b)(1). The various test system components should incorporate the same proprietary name (ABC blood glucose test system, ABC blood glucose meter, ABC blood glucose test strips, etc.) to aid in identification of system components.
2. You must include the intended use of the product. 21 CFR 809.10(a)(2) and 21 CFR 809.10(b)(2). You should specify that the device is for prescription-use.
3. Labeling must include the chemical, physical, physiological, or biological principles of the procedure as per 21 CFR 809.10 (b)(4). The discussion of these principles should include identification of the enzyme and description of the reaction. Labeling should clarify whether results are determined in terms of whole blood or plasma equivalents. BGMS devices intended for use in the U.S., should report results in terms of plasma equivalents
4. The labeling must provide instructions for specimen collection and preparation. Instructions should include a statement to users on the importance of thoroughly washing and drying the skin before taking a sample, because contaminants on the skin may affect results as per 21 CFR 809.10(b)(7).
5. You must include a statement of limitations of the procedure. Labeling should state known extrinsic factors or interfering substances affecting results as per 21 CFR 809.10(b)(10). This should include, but is not limited to, the following:
 - a. Labeling should include testing conditions that may cause clinically significant errors (due to bias or imprecision) with your device (e.g., specific drugs, oxygen therapy, testing with venous, arterial, or neonatal blood, high altitude, or EMC interference). Sponsors should indicate the most extreme conditions (e.g., the highest altitude) at which device should be used based on the results of performance testing.

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- b. You should describe clinical situations in which the BGMS performance may not be acceptable. For example, FDA recommends statements such as the following: Critically ill patients should not be tested with a glucose meter because results may be inaccurate. Inaccurate results may occur in severely hypotensive individuals or in dehydrated patients or patients in shock. Inaccurate results may occur for individuals experiencing a hyperglycemic-hyperosmolar state, with or without ketosis.
- c. Labeling should include limitations against alternative site and tight glycemic control use (unless appropriate studies are performed and included in the 510(k)). Labeling should also state that results from alternative sampling sites should not be used to calibrate continuous glucose monitoring systems (CGMS) or entered into insulin dose calculators for dosage recommendations.
6. You must provide appropriate storage instructions adequate to protect stability of the product. 21 CFR 809.10 (b)(5)(iv). This type of information should be provided for all components of the system including control solutions, test strips, etc.
7. Labeling must describe details of calibration and of quality control procedures. 21 CFR 809.10(b)(8)(v) and 21 CFR 809.10(b)(8)(vi). This is to help ensure optimal performance of the system.
8. Labeling must include expected values. 21 CFR 809.10(b)(11). FDA recommends that the expected values in the package insert should be those for non-diabetics. FDA does not recommend including additional ranges adjusted for diabetics because such ranges are individualized and determined by the clinician. The expected values should be cited from in-house studies or up-to-date reference sources.
9. Labeling must include specific performance characteristics. 21 CFR 809.10(b)(12). Sponsors should briefly describe all studies and summarize results in the package inserts. FDA recommends that this include performance data summaries from in-house and user studies. For presentation of accuracy in particular, see the charts, below for an example. Performance should be presented separately for each anatomical site, matrix (arterial, capillary, etc.) and any specific claims (e.g. neonatal).

We recommend the following types of presentations to represent the results of your accuracy studies in user manuals and package inserts.

Suggested Representation of Accuracy for Prescription-use Only Devices – Example:

The [XYZ] meter and [XYZ] reagent strips for the [XYZ] monitoring system were tested on 350 capillary blood samples, and the results were compared to the laboratory method (e.g., YSI). The tables show differences in glucose values between the XYZ device and YSI. The first table represents samples for glucose results lower than 70 mg/dL (by the XYZ method). The second table represents samples for glucose results greater than or equal to 70 mg/dL.

Glucose results lower than 70 mg/dL

Difference range between laboratory reference method and the XYZ method	Within +/- 5 mg/dL	Within +/- 7 mg/dL	Within +/- 10 mg/dL	Within +/- 15 mg/dL
The percent (and number) of samples for which the difference between the XYZ device and ABC laboratory method were within the difference range shown in the top row.	90% (126/140)	99% (139/140)	99% (139/140)	100% (140/140)

Glucose results greater than or equal to 70 mg/dL

Difference range between the laboratory reference method and the XYZ value.	Within +/- 5%	Within +/- 10%	Within +/- 15%	Within +/- 20%
The percent (and number) of samples for which the difference between the XYZ device the ABC laboratory method were within the difference range shown in the top row.	80% (168/210)	99% (208/210)	99% (208/210)	100% (210/210)

The tables show that 347 (139+208) of the 350 samples met the defined acceptance criteria.

Note: When glucose meter results are compared to the laboratory results, difference values below 70 mg/dL are expressed in mg/dL, while those greater than or equal to 70 mg/dL are compared in percent.

10. You must describe the principles of operation for the instrument as well as service and maintenance information. 21 CFR 809.10(b)(6). Labeling should include a list or summary of error messages, descriptions of what those error messages mean, and appropriate troubleshooting procedures for those error messages.

11. Labeling must include statements of warning or precautions as appropriate to the hazard presented by the product on the outer container and the insert. 21 CFR 809.10(b)(5)(ii), and 21 CFR 809.10(a)(4).

You should clearly and prominently state the important warnings for your devices, for example in a section entitled **Important Safety Instructions**. You should stress the risk of disease transmission when using BGMS devices and reference any relevant public health notifications, standard practice guidelines, or other resources available to users. At a minimum, the following warnings should be included:

- Users need to adhere to Standard Precautions when handling or using this device. All parts of the glucose monitoring system should be considered potentially infectious and are capable of transmitting blood-borne pathogens between patients and healthcare professionals. For more information, refer to “2007 Guideline for

Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings",
<http://www.cdc.gov/hicpac/2007ip/2007isolationprecautions.html>.

- The meter should be disinfected, following the manufacturer's instructions, after use on each patient. This Blood Glucose Monitoring System may only be used for testing multiple patients when Standard Precautions and the manufacturer's disinfection procedures are followed.
- Only auto-disabling, single use lancing devices may be used with this device.

In the section describing **how to obtain a blood sample** (see also item 2, above, regarding sample collection), you should re-iterate the risk of bloodborne pathogen transmission and state that only an auto-disabling, single use lancing device should be used. We recommend that you incorporate Standard Precautions and practices in your instructions. Include any graphics demonstrating correct blood draw procedures and ensure that the pictures show users wearing gloves.

In addition, we recommend that you refer users to the following practice guidelines:

"Biosafety in Microbiological and Biomedical Laboratories (BMBL)",
<http://www.cdc.gov/biosafety/publications/bmbl5/>

"Protection of Laboratory Workers From Occupationally Acquired Infections" CLSI (Clinical Laboratory Standards Institute) Document M29-A3.

You should stress that the operator should wear a new pair of clean gloves before testing each patient.

12. You must include a step-by-step outline of procedures, 21 CFR 809.10(b)(8)

The user manual should contain detailed instructions for how users are to perform **disinfection procedures** for the meter **between patients**. This information should be based on the validation studies performed as described above in Section IV. You should also include the following:

- An explanation of why the cleaning and disinfection should be performed.
- The recommended frequency of disinfection, i.e. between each patient.
- The materials needed for disinfection and how they can be purchased or prepared.
- A detailed procedure describing what parts of the device should be cleaned and disinfected, what should not be disinfected (avoided), the amount of time the disinfectant needs to remain on the meter (contact time), etc. You should include graphics/photographs to assist the user. Again, be sure that all graphics show the user wearing gloves.
- A statement that after disinfection, users' gloves should be removed and hands cleaned before proceeding to the next patient.

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- A contact telephone number for technical assistance or questions should be prominently listed in the cleaning and disinfection section.

We recommend you also include the references below:

“FDA Public Health Notification: Use of Fingertick Devices on More than One Person Poses Risk for Transmitting Bloodborne Pathogens: Initial Communication”
<http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm224025.htm>

“Infection Prevention during Blood Glucose Monitoring and Insulin Administration”,
<http://www.cdc.gov/injectionsafety/blood-glucose-monitoring.html>

Appendix 1. Potential Sources of Error to Consider for BGMS Devices

The following table lists potential sources of error associated with the design, production, and use of BGMS devices. We do not intend for this to be a complete list. You should consider all sources of error based on your knowledge of your specific device. Documents such as CLSI EP-18A [7] and ISO 14971 [1] also provide lists of preanalytical, analytical, and post-analytical errors to consider.

Table 7 – Examples of Potential Sources of Error

Category	Source of error or failure
Operator	<p>Failure to follow procedure correctly, for example:</p> <ul style="list-style-type: none">• Sample contamination• Incorrect specimen collection (e.g., poor lancing technique and incorrect volume)• Application of an insufficient amount of blood to the strip or incorrect application of blood to strip• Use of a sample from an alternate site not validated by the manufacturer• Application of the specimen to the strip more than once (for example, if the user believes not enough specimen was added the first time)• Incorrect insertion of strip into meter• Inaccurate timing• Use of contaminated, outdated, or damaged strips or reagents, including calibrators or quality control materials• Failure to understand or respond to meter output.• Errors in meter maintenance or cleaning• Errors in calibration or failure to calibrate or otherwise adjust the meter or check performance with quality control materials, as directed by labeling• Incorrect saving or use of stored data• Improper storage or handling of the meter, calibrators, quality control materials or test strips, or maintenance of the meter• Inadvertent changes of parameters (such as units of measurement)• Failure to contact physician when necessary (OTC)• Incorrect incorporation of results into overall treatment plan (prescription-use)• Use of strips not validated for use on the monitor

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Reagent	<ul style="list-style-type: none"> • Expired strips or reagents • Damaged or contaminated strip • Failure of strips, calibrators, or quality control materials to perform adequately • Incorrect manufacturing; product fails to conform with specifications • Incorrect dimensions of reagent strip • Interference with chemical reaction on strip (e.g., reducing substances) • Inadequate design of container for strips or other reagents; failure to prevent deterioration; failure of desiccant used to keep strips dry
Environmental	<ul style="list-style-type: none"> • DEVICE EFFECTS <ul style="list-style-type: none"> • Temperature • Humidity • Altitude; hyperbaric conditions • Electromagnetic radiation • Visible light; sunlight • HUMAN FACTORS <ul style="list-style-type: none"> • Lighting, glare off meter surfaces • Distractions, visual and auditory • Stressful conditions • Limited manual dexterity
Software	<ul style="list-style-type: none"> • Confusing or obscure user prompts and feedback • Incorrect mathematical algorithm • Undetected or unrecognized signal errors • Timing failure • Incorrect storage of test results in memory, including matching result with correct patient or time of test • Other software failures
Hardware	<ul style="list-style-type: none"> • Electronic failure • Physical trauma or vibration • Damage to the device from incorrect strip dimensional tolerances (third party manufacturer) • Electrostatic discharge • Electromagnetic/radiofrequency interference • Battery reliability, lifetime, and replacement • Component(s) failure

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	<ul style="list-style-type: none">• Incorrectly manufactured
System	<ul style="list-style-type: none">• Physical trauma or vibration• Incorrect calibration/adjustment (between lots of strips)• Calibration failure, interference, instability or use beyond the recommended period of stability.• Labeling not geared to intended user.• Meter or operation complexity not geared to intended user• Inadequate training
Clinical	<ul style="list-style-type: none">• Interference from endogenous substances.• Severe conditions (e.g., dehydration, hypoxia, hyperglycemic-hyperosmolar state, hypotension or shock, ketoacidosis).• Interference from other sugars (e.g., maltose intravenous solutions)

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Appendix 2. Special 510(k)s and BGMS Devices

What is a special 510(k) and how does it apply to your blood glucose meter submission?

A special 510(k) submission is an alternative to the traditional method of demonstrating substantial equivalence for certain modifications that do not alter the intended use or fundamental scientific technology of the device. For such modifications, the Agency believes that the rigorous design control procedure requirements outlined in the Quality System Regulation (QS reg) [See 21 CFR 820] produce highly reliable results that can form, in addition to the other 510(k) content requirements, a basis for the substantial equivalence determination.

As such, under the special 510(k) option, a manufacturer who is intending to modify his/her own legally marketed device will perform and present the risk analysis and the necessary verification and validation activities to demonstrate that the design outputs of the modified device meet the design input requirements. Once the manufacturer has ensured the satisfactory completion of this process, a "Special 510(k): Device Modification" may be submitted.

Eligibility for a Special 510(k):

To determine whether a modified BGMS device is eligible to be submitted as a special 510(k), you should consult the FDA Guidance Document entitled "The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications - Final Guidance" which can be found at:
www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080187.htm. Sponsors should also consult the document "How to Prepare a Special 510(k)" at:
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm134573.htm>

As noted above, to be eligible for a special 510(k), the manufacturer should be modifying its own legally marketed device. This usually means that the candidate device and predicate device are part of the same device design file. *Similarities* between the candidate and predicate devices alone do not necessarily mean that the candidate device is a modification of the predicate device.

FDA believes that to ensure the success of the Special 510(k) option, there should be a common understanding of the types of device modifications that may gain marketing clearance by this path. In this vein, it is critical that Industry and Agency staff can easily determine whether a modification is appropriate for submission as a Special 510(k). To optimize the chance that a Special 510(k) will be accepted and efficiently reviewed, 510(k) submitters should evaluate each modification to insure that the device modification does not: (1) affect the intended use or (2) alter the fundamental scientific technology of the device.

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Based on FDA's experience with blood glucose meters, we can offer the following list of modifications that may or may not be eligible for review as a special 510(k). This list is not intended to be all-inclusive.

Modifications that are generally eligible for a special 510(k):

- Minor changes in user interface
- Addition of data transfer capability (e.g., adding the ability to transmit glucose results to a personal computer)
- Change in memory capabilities (e.g., adding the ability to store additional results)
- Elimination of strip coding requirements
- Addition of a voice (speaking) feature if the device is not intended for visually impaired users

Modifications that are generally NOT eligible for a special 510(k):

- Significant change in the sample volume applied to the glucose test strip
- Addition of alternate sampling sites (e.g., adding the palm in addition to the fingertip)
- Addition of sample matrices (e.g., adding venous blood in addition to capillary blood)
- Change to the measuring algorithm used to calculate a glucose concentration
- Change in enzyme used in the chemical reaction (e.g. from glucose dehydrogenase to glucose oxidase)
- Any other modification that affects the intended use of the device
- Any other change in fundamental scientific technology

We recommend that you contact OIR to discuss any specific questions you have regarding your BGMS device's eligibility to be submitted as a special 510(k).